Remarks

Claims 126-129, 131, 135-139, 144, 148-156 are pending; claims 135-139 and 151-156 are withdrawn; claims 1-125, 130, 132-134, 140-143 and 145-147 are canceled; claims 126-131, 144, and 148-150 are rejected; and claims 157-159 are added. Each of the rejections is addressed below.

Support for the Amendments

Amendments to the specification include insertion of ™ and ® as necessary and to correct obvious typographical errors. No new matter is added.

Support for the amendments can be found throughout the specification and in the previously pending claims. For example, support for the amendment to claims 126, 144, 151, 152, and 153 of the polypeptide being present in a pharmaceutically acceptable carrier can be found in former claim 130 or in the specification on page 25, lines 21-23. Support for identity referring to sequence identity is supported. for example, in the specification on page 13, lines 20-24 or page 15, lines 24-30, or page 22, lines 6-8. Support for newly added claims 157 to 159 can be found, for example, in the specification on page 17, line 23-page 18, line 10, particularly page 18, lines 4-10.

Amendment and cancellation of the claims here are not to be construed as an acquiescence to any of the rejections/objections made in the instant Office Action or in any previous Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed, or substantially similar claims in one or more subsequent patent applications.

Objection to the Specification

The Examiner's objection to the specification is overcome by the present amendment.

Use of Trademarks

The Examiner notes that the application includes trademarks. Applicant thanks the Examiner for the careful reading of the application. Applicant acknowledges that such trademarks must be capitalized, and have reviewed the specification for compliance with this requirement and have amended the specification as indicated above.

Sequence Listing

The Examiner notes that the sequence depicted in Figure 1D is inconsistent with the amino acid sequence listed in the sequence listing filed October 27, 2006. Applicant has reviewed sequence 27 and found that it is the same as the sequence presented in Figure 1D. Withdrawal of the objection is requested. However, if the Examiner maintains the rejection, Applicant requests that the specific error be pointed out in the next Office Action.

Lack of Antecedent basis

The Examiner has objected to the specification for not providing proper antecedent basis for the terms "bacterial cell is present in a sample, and the method identifies" and "cell is present in a patient." Applicant respectfully disagrees. Applicant specifically points to page 18, lines 24-26, reproduced below, to support claim 128 and newly added claim 159.

> They also find utility in the recovery from various samples of culturable microorganisms (e.g. from soil, food, marine, freshwater, or tissue samples) or from samples taken from an organism (e.g. a human or animal). page 18, lines 24-26)

Applicant points to page 33, first paragraph, and page 34, lines 20-26, each reproduced below, for support of claim 129.

> Thus, the materials of the invention find general application as antimicrobial agents, for example as antibacterial agents. They may therefore be used in the treatment, prophylaxis or diagnosis of microbial (e.g. bacterial) infections, particularly those infections associated with latency (e.g. mycobacterial infections). (page 33, lines 1-5)
> .....
> In another aspect, the invention may be used to resuscitate or assist in resuscitating (or activate or assist in activating) a latent (dormant) pathogenic microbe in vivo thereby to potentiate adjunctive antimicrobial therapy. The adjunctive antimicrobial therapies for use in such applications are those which depend for full efficacy on a non-latent or active (e.g. growing or replicating) target pathogen population (for example adjunctive therapies based on certain types of antibiotic). Thus, the materials of the invention may act synergistically with various antimicrobial compounds in antimicrobial therapy. (page 34, lines 20-26)

Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 126-131, 144, and 148-150 are rejected under 35 U.S.C. § 112, first paragraph for lacking enablement with regard to scope. For the reasons detailed below, Applicants respectfully disagree with the rejections under 35 U.S.C. § 112, first paragraph, which should be withdrawn.

At page 4, paragraph 18, of the Office action mailed on June 9, 2008, the Examiner acknowledges that Applicant has identified RP factor proteins from *Micrococcus luteus* cells, and from *Mycobacterium tuberculosis*, including SEQ ID NO: 2. RP factors have also been identified from *M. leprae*, *Streptomyces coelicolor*, *Streptomyces rimosus*, *Mycobacterium smegmatis*, *Mycobacterium bovis*, and *Corynebacterium glutamicum* using an RP-factor of *M. luteus*. The Examiner does not disagree with the noted assertion of the Applicant that one of skill in the art would be able to recognize peptides that fall within the scope of the claims having 20% to 50% sequence identity 117-184 of SEQ ID NO:2, or any other sequences claimed. The Examiner asserts that the passages indicated by the Applicant in the previous response to Office Action did not correspond to the matter discussed in the response. Applicant was referring to pages and lines in the PCT publication rather than the version of the application filed in the USPTO on October 25, 2001. Line and page numbers cited herein refer to that document. Figure and Table numbers are the same in the two documents.

The Examiner is pointed to the following pages and lines for each of the points under paragraph 18.

(A) RP factor proteins from other bacteria, including SEQ ID NO: 2 have been identified. Page 50, line 8 to page 51, line 6.

(B) RP factors have been identified from specific bacteria. Page 39. lines 9-17.

(C) Alignment of RP factors reveals specific structural features. Page 43, line 29 to page 44, line 2; and page 51 line 8 to page 52, line 5.

(E) Methods are provided in the specification for assaying claimed peptides of the invention. Page 45, line 16 to page 46, line 10; and page 52, lines 7-24.

(F) SEQ ID NO: 2 has a biological function. Page 52, lines 7-24.

The number of living cells in a bacterial culture is typically assayed by measuring the ability of the cells to grow and divide on an agar bacterial culture plate (page 2, lines 22-23). Certain bacterial cells may exist in a "dormant" "latent" or "moribund" state, where they cannot be cultured on agar plates under standard growth conditions (page 2, lines 24-26). Such cells are not dead, however, because they can be resuscitated (i.e., induced to grow in culture) (page 2, lines 27-28). The existence of "latent" pathogenic bacteria has important implications for human health related to bacterial infection (page 3, lines 5-7). The pathogenic bacteria, *M. tuberculosis*, for example, persists for long periods of time in a "latent" state that is difficult to detect in standard diagnostic methods (page 3, lines 7-14).

The Examiner alleges that Applicants have failed to provide guidance regarding where amino acid substitutions may be made in the polypeptide. Applicant respectfully disagrees. Using sequence information relating to *M. luteus* RP-factor, Applicant has identified RP factor proteins from other bacteria, including SEQ ID NO:2 from *M. tuberculosis*, that share sequence identity with *M. luteus* RP-factor (page 50, line 10, to page 51, line 6, under the header "Identification of RP-factor homologues"), and Applicant has used this information to identify conserved structural features. Specifically, Applicant has identified two RP-factors from *M. luteus* and one from *M. tuberculosis* (Figure 1A; page 34, line 21, to page 35, line 4). In addition, Applicant has identified RP-factors from *M. leprae* and *Streptomyces coelicolor*, *Streptomyces rimosus, Mycobacterium smegmatis,* which includes four similar genes, *Mycobacterium bovis,* and *Cornebacterium glutamicum,* which includes two similar genes (Figure 1A; page 50, line 10, to page 51, line 6). Applicant has provided an alignment of RP factor proteins in Figure 1A, which identifies conserved structural features and highly conserved amino acid residues (page 51, line 10 to page 52, line 2; Figures 9A and 9B). Applicants found that RP-factors share a secretory signal sequence and a conserved 70-residue segment that may act as a signaling domain (page 51, lines 10-21, under the heading "Domain structure"). This domain includes four conserved tryptophan residues and two conserved cysteine residues that may form a disulfide bridge (page 51, line 28 to page 52, line 2). These structural features are conserved among a wide variety of proteins and are, therefore, likely to be functionally important. Accordingly, Applicant's specification provides guidance relating to those regions of

the protein where sequence variations are likely to be tolerated and those conserved regions where variations in the sequence are less desirable.

Moreover, one of skill in the art could readily identify those variant polypeptides that fall within the scope of Applicants' claims. For example, Applicants' specification clearly describes methods of screening for polypeptides capable of resuscitating dormant bacteria using purified RP-factors (page 52, line 9, to page 53, line 11, page 55, line 16 to page 56, line 20). Such screening does not constitute undue experimentation because it could easily be accomplished using standard techniques that are plainly described in Applicant's specification. In analyzing what constitutes undue experimentation, the MPEP (§ 2164.06) cites *In re Wands*, (858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988)):

> The determination of what constitutes undue experimentation in a given case requires application of a standard of reasonableness, ***having due regard for the nature of the invention and the state of the art.*** *Ansul Co. v. Uniroyal, Inc.* (citation omitted). The test is not merely quantitative because a considerable amount of ***experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*** (pg. 1404)

The present situation is, in all important aspects, indistinguishable from the facts in *Wands* in which the Federal Circuit held that the applicant's claim was enabled, despite the necessity for screening, because the process of screening was straightforward. Applicant notes that in *Wands*, the methods claimed required the use of a monoclonal antibody. During prosecution Wands submitted a declaration under 37 C.F.R. §1.132 providing information about all of the hybridomas that Appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas.

Of all of the fusion experiments performed by Wands, only four of the nine fully characterized hybridomas produced antibodies that fell within the scope of the claims. Wands did not teach an improved method for making hybridomas. Wands taught and claimed a method that required the use of hybridomas having specific claimed characteristics. An additional 134 hybridoma lines were frozen and stored without further analysis. The number of these hybridomas that produce antibodies that fall within the limitations of the claims is unknown.

Wands demonstrates that routine experimentation is not always trivial or successful. Routine experimentation can include animal testing. Routine experimentation, by the nature of it being experimentation, has some aspect of uncertainty in regard to result, which is tolerable within the scope of enablement. If the experimental path and data analysis have sufficient certainty (i.e., are routine), the claims are enabled. Wands makes it clear that not all outcomes from routine experimentation need to fall within the scope of the claims in order for the claims to be enabled. The assertion in the Office Action that "assigning functional activities for any particular protein or family of proteins based on sequence homology in inaccurate, partly because of the multifunctional nature of proteins." Applicant submits that based on the level of success of Wands, not every peptide that falls within the scope of the claims need have the claimed activity. The Office Action notes that "Table 2 and Experiment III show that a *M. luteus* Rp-factor was able to stimulate the growth of *M. tuberculosis* cells that failed to show viability." Therefore, the Examiner admits that the specification provides enabling disclosure for the testing of peptides for the claimed activity. Applicant submits that using no more than routine methods, such as those provided in the specification, the skilled artisan could readily identify those polypeptides having at least 20% identity to SEQ ID NO:2 that are capable of resuscitating dormant bacteria, assigning function, or not, to protein sequences.

Moreover, the additional data provided by the Applicant in Exhibit A in the previous response demonstrates that testing methods for activity of peptides as RPs is routine in the art. The data also demonstrate that peptides with very low sequence identity to SEQ ID NO: 2 can have RP activity.

In support of the enablement rejection, as it applies to claims 128-131, the Examiner alleges that Applicants have failed to enable the use of polypeptide variants of SEQ ID NO:2 in therapy, prophylaxis, or diagnosis. Applicants disagree and traverse the rejection. Nevertheless, the claims are now directed to methods for identifying a microbial infection in a sample (claim 128) and to methods for resuscitating a bacterial cell where the cell is present in a patient being treated with an antimicrobial. Applicants have clearly shown that RP-factors may be used to resuscitate bacterial cells, including dormant *M. tuberculosis* cells isolated from a mouse infected with *M. tuberculosis* (page 58, line 1, to page 59, line 19). At Table 2, in Experiment III, Applicants showed that an RP-factor was able to stimulate the growth of *M. tuberculosis* cells

that failed to show signs of viability (Table 2). In view of this disclosure, Applicants have clearly enabled methods of resuscitating bacterial cells in a sample or a patient.

The Office Action notes that the claims 128 and 129 are drawn to an isolated, but not purified protein. Applicant notes that the independent claims have been amended to recite that the protein is present in a pharmaceutically acceptable carrier such that the compositions may be administerable to a subject. Applicant further notes that dependent claims have been added reciting that the polypeptide is purified essentially to homogeneity. Therefore, the composition would be acceptable for administration to a subject.

The Office Action appears to allege that a lack of understanding of the precise mechanism of action of RP factors makes the claims non-enabled (pages 8 and 9). Applicant respectfully disagrees. The ability to test a peptide to determine if any particular peptide would be useful for the claimed methods is not dependent on understanding the mechanism of action of the peptide. One of skill in the art can determine if there is or is not growth without understanding why there may or may not be growth of bacteria. Wands does not require an understanding of mechanism regarding the precise mode of functioning of an invention as long as one can test the invention and determine that it does or does not function.

Thus, this basis for the enablement rejection should also be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 126, 127, 130, 131, 144, 148, and 149 are rejected under 35 U.S.C. § 102(b) as anticipated by Mukamolova et al., (Antoine van Leewwenhoek 67:289-295, 1995), as evidenced by Mukamolova et al., (PNAS 95:8916-8921, 1998). Applicants respectfully disagree and traverse the rejection.

Applicant has amended claims 126, 144, 151, 152, and 153 to recite that the claimed polypeptide is present in a pharmaceutically acceptable carrier, the limitation of claim 130 which is also included in the instant rejection. The Examiner asserts that Mukamolova et al. 1995 teaches that "The antibacterial factor secreted or expressed by the *Micrococcus luteus* cells is separated from the cells and therefore isolated. The sterile supernatant containing the non-cellular or isolated antibacterial factor is contained in minimal medium, i.e., a pharmaceutically

acceptable carrier suitable for local administration." Applicant respectfully disagrees that minimal media could be considered a "pharmaceutically acceptable carrier."

Filtered minimal media from the bacterial culture would include any of a number of proteins and peptides secreted by the bacteria, as well as proteins from dead, lysed bacteria. Applicant submits that the numerous non-self proteins could result in a massive immune response, particularly upon repeat administration. Applicant submits that any sterile solution cannot be used as a "pharmaceutically acceptable carrier". Moreover, even if one were to purify the protein, for example, per the methods in Mukamolova et al. 1998, the resulting protein would not be in a pharmaceutically acceptable carrier as now claimed. It is noted in the third to last sentence in column 2 on page 8917 of the reference, that for retention of activity, the fractions were dialyzed against buffer 2, which is 10 mM Tris-HCl, pH 7.4, and 10% glycerol containing 0.08 M KCl. Such a buffer would not be acceptable for injection. As the buffer is stated to be required for activity of the protein, one would not be discouraged from altering the composition of the buffer. Therefore, the Mukamolova et al. 1995 reference cannot anticipate the claims, either alone or with the support of the Mukamolova et al. 1998 reference.

Applicant has amended claims Thus, the rejection of the claims under 35 U.S.C. § 102(b) should be withdrawn.

Rejections under 35 U.S.C. § 112, ¶1

Claims 128 and 129 are rejected under 35 U.S.C. §112, first paragraph for containing new matter. Claim 128 has been amended as set forth above to recite that the bacterial cell is present in a sample. This language finds support, for example on page 18, lines 24-26 of the specification. Claim 129 is supported as set forth above.

The rejection for new matter is overcome. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, ¶2

Claims 128, 129, 148, and 149 are rejected under 35 U.S.C. §112, ¶2 for lacking clarity. The claims have been amended as set forth above to further clarify the matter claimed.

Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Applicants authorizes a fee for an extension of time of two months and a Request for Continued Examination with the instant application. It is believed that no further fee is due. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 04-1105, referencing case number 60261(49946).

Dated: October 16, 2008

Respectfully submitted,

By: /Colleen McKiernan/
Colleen McKiernan, Ph. D.
Registration No.: 48, 570
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5555
Attorneys/Agents For Applicants